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Wave Life Sciences

Corporate Presentation

March 2, 2020

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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Building a leading genetic medicines company

INNOVATIVE PLATFORM

- Stereopure oligonucleotides
- Backbone modifications
- Allele-selectivity
- Novel modalities (ADAR)
- Foundational stereochemistry IP

FOUNDATION OF CNS PROGRAMS

- Huntington’s disease
- ALS / FTD
- Ataxias
- Parkinson’s
- Alzheimer’s

PRISM™

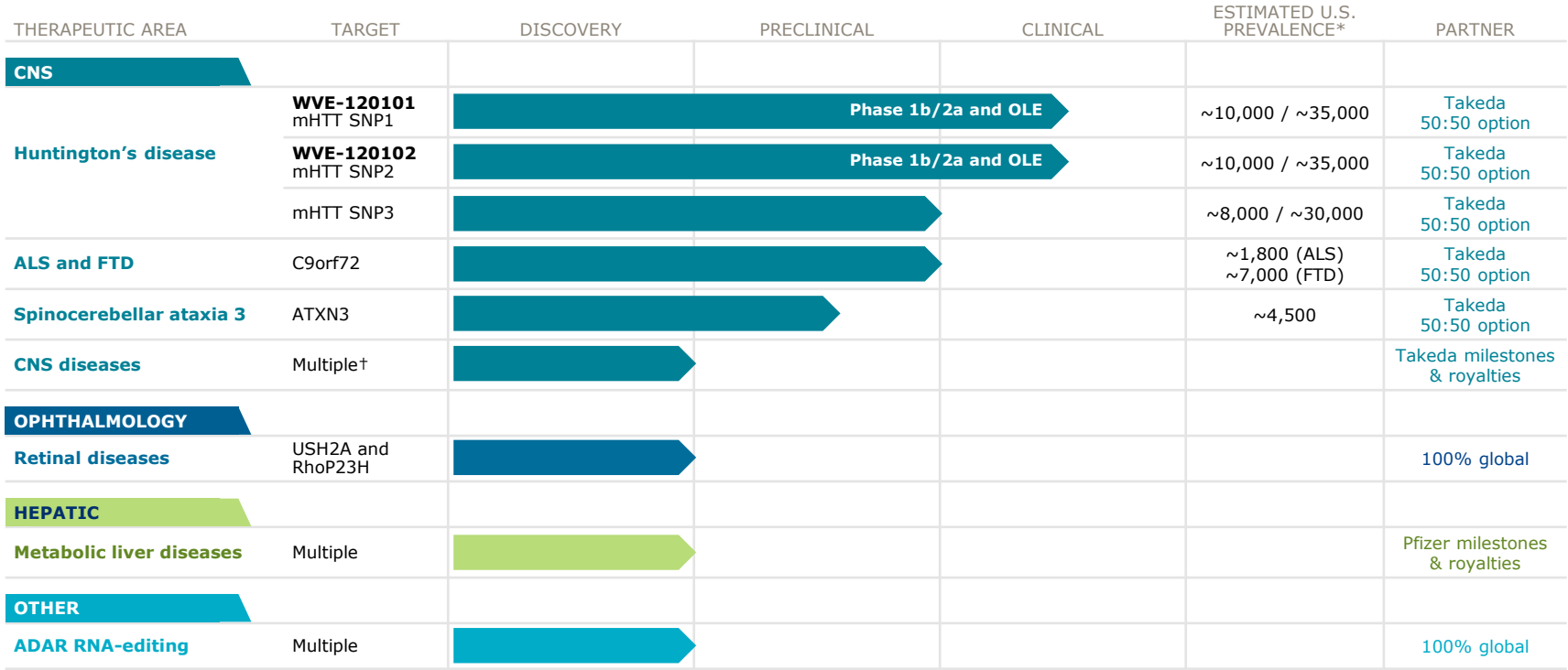
CLINICAL DEVELOPMENT EXPERTISE

- Multiple global clinical trials ongoing across eight countries
- Innovative trial designs

MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

Innovative pipeline led by CNS programs



*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate; for Huntington's disease, numbers approximate manifest and pre-manifest populations, respectively.
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; CNS: Central nervous system; OLE: Open-label extension

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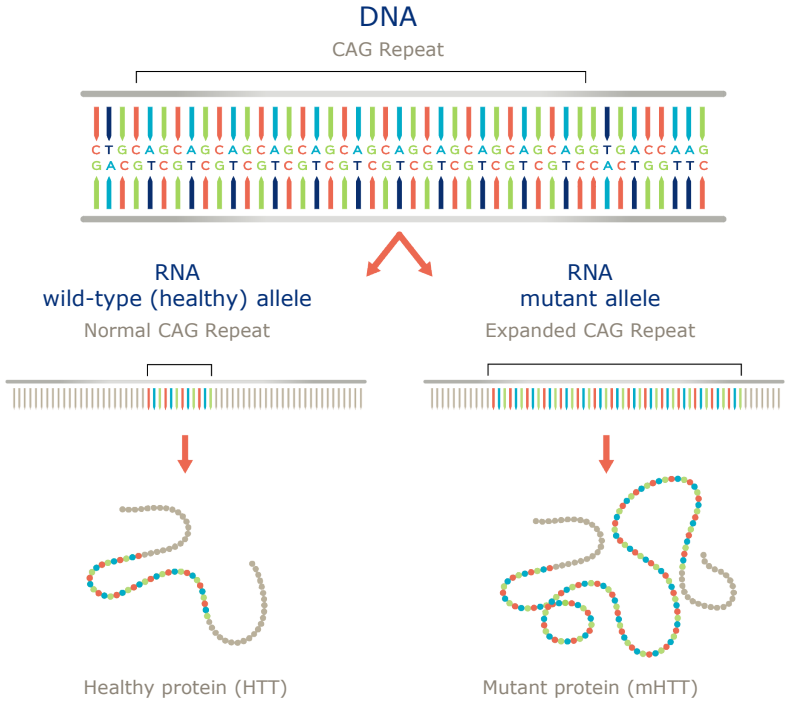
HD portfolio
Huntington's Disease

Huntington's disease: a hereditary, fatal disorder

- Autosomal dominant disease, characterized by cognitive decline, psychiatric illness and chorea; fatal
- No approved disease-modifying therapies
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT); accumulation of mHTT causes progressive loss of neurons in the brain
- Wild-type (healthy) HTT protein critical for neuronal function; evidence suggests wild-type HTT loss of function plays a role in Huntington's disease
- 30,000 people with Huntington's disease in the US; another 200,000 at risk of developing the condition



Sources: Auerbach W, et al. *Hum Mol Genet.* 2001;10:2515-2523. Dragatsis I, et al. *Nat Genet.* 2000;26:300-306. Leavitt BR, et al. *J Neurochem*. 2006;96:1121-1129. Nasir J, et al. *Cell*. 1995;81:811-823. Reiner A, et al. *J Neurosci.* 2001;21:7608-7619. White JK, et al. *Nat Genet*. 1997;17:404-410. Zeitlin S, et al. *Nat Genet*. 1995;11:155-163. Carroll JB, et al. *Mol Ther.* 2011;19:2178-2185. HDSA 'What is Huntington's disease?' https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/ Accessed: 11/2/18.; Becanovic, K., et al., Nat Neurosci, 2015. 18(6): p. 807-16. Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005. 14(10): p. 1379-92.; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006. 7: p. 80.

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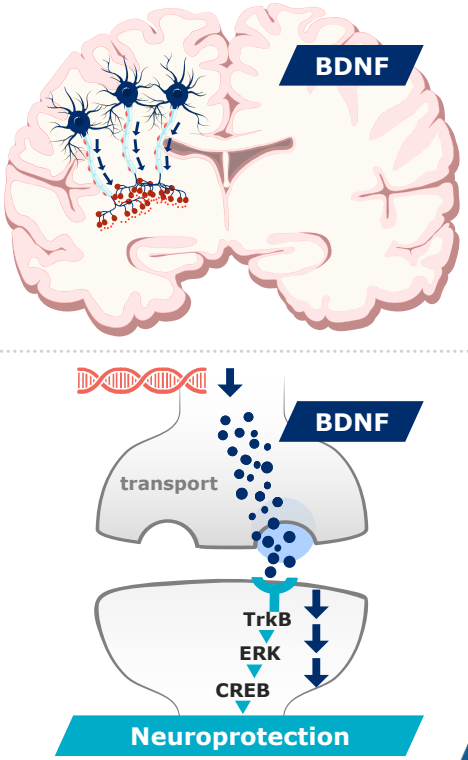
Importance of wild-type huntingtin (wtHTT) in HD

Huntington's disease (HD) may be caused by a dominant gain of function in mutant HTT *and* a loss of function of wtHTT protein

- Evidence suggests wild-type or healthy HTT is neuroprotective in an adult brain
  - Transport of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) are regulated by wtHTT levels
- Relative proportion of wild-type to mutant protein is critical
  - Increased amount of wild-type protein relative to mutant HTT may result in slower disease progression (measured by age-at-onset)
  - Patients with lack of wild-type have significantly more severe disease (measured by disease progression after symptom onset)



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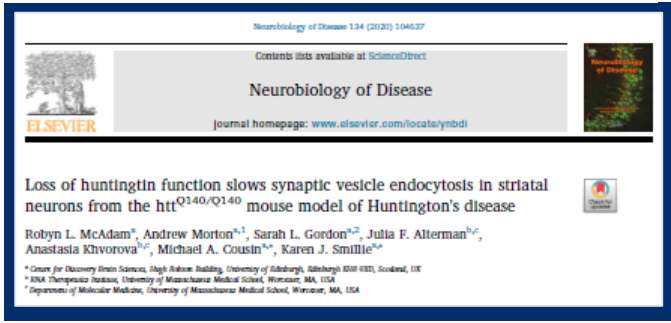
Sources: Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006; Becanovic, K., et al., Nat Neurosci, 2015; Saudou, F. and S. Humbert, The Biology of Huntingtin. Neuron, 2016; Gauthier, L.R., et al., Cell, 2004; Caviston, J.P. and E.L. Holzbaur, Trends Cell Biol, 2009; Ho, L.W., et al., J Med Genet, 2001, Zuccato et al., Science 2001; Zuccato et al., Brain Pathol 2007; Marullo et al. Genome Biol 2010; Squitieri et. al, Brain 2003

Increasing evidence on the importance of wtHTT in HD pathogenesis, CNS and systemic health

Recent publications on wtHTT LoF as a likely driver of HD pathogenesis


Neurobiology of Disease 134 (2020) 104637

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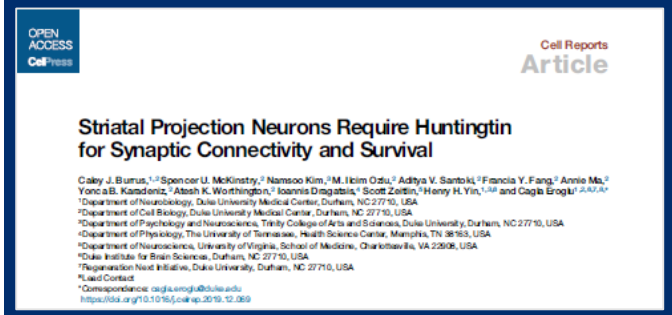
Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Loss of huntingtin function slows synaptic vesicle endocytosis in striatal neurons from the htt$^{Q140/Q140}$ mouse model of Huntington's disease

Robyn L. McAdam[a], Andrew Morton[a,1], Sarah L. Gordon[a,2], Julia F. Alterman[b,c], Anastasia Khvorova[b,c], Michael A. Cousin[a,*], Karen J. Smillie[a,*]

- Striatum-specific defect in synaptic vesicle endocytosis that was not corrected by total lowering of HTT
- Corrected by overexpression of wild-type protein


OPEN ACCESS CellPress

Cell Reports

Article

Striatal Projection Neurons Require Huntingtin for Synaptic Connectivity and Survival

Caley J. Burrus,[1,2] Spencer U. McKinstry,[2] Namsoo Kim,[3] M. Ilcim Ozlu,[2] Aditya V. Santoki,[2] Francia Y. Fang,[2] Annie Ma,[2] Yonca B. Karadeniz,[2] Atesh K. Worthington,[2] Ioannis Dragatsis,[4] Scott Zeitlin,[5] Henry H. Yin,[1,6,8] and Cagla Eroglu[1,2,6,7,9,*]

- Striatal projection neurons require HTT for motor regulation, synaptic development, cell health, and survival during aging
- Loss of HTT function could play a critical role in HD pathogenesis

wtHTT in HD highlighted at CHDI 15th Annual HD Therapeutics Conference:

HTT LOWERING: EXPLORING DISTRIBUTION, TIMING, AND SAFETY (LOSS OF FUNCTION)

Key points discussed at meeting:

- wtHTT has numerous critical functions throughout life (e.g., intracellular trafficking, cell-cell adhesion, BDNF transport)
- Near elimination of mouse wtHtt detrimental regardless of when suppression begins
- Specific brain regions, e.g., STN, may be particularly vulnerable to wtHTT lowering
- Mouse Htt lowering can lead to thalamic, hepatic, pancreatic toxicity
- HTT LoF mutations highly constrained in human population, suggesting selection against LoF mutations

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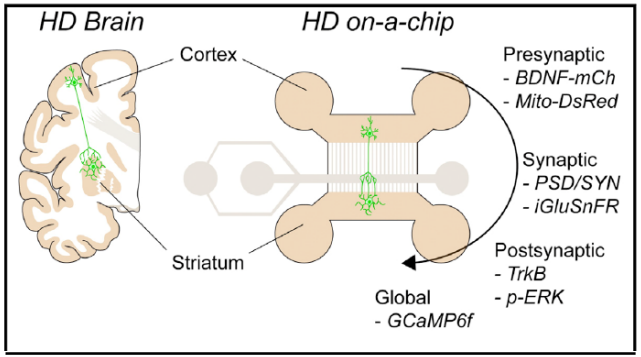
LoF: Loss of function; wtHTT: wild-type huntingtin; HD: Huntington's disease; STN: subthalamic nucleus

Wild-type HTT in the cortex appears critical for striatal health



Neuron Type	Genetic Status				Compartment
Cortical	WT	WT	HD	HD	Presynaptic
Striatal	WT	HD	HD	WT	Synaptic / Post-synaptic
Network Status	*Functional*		*Dysfunctional*		

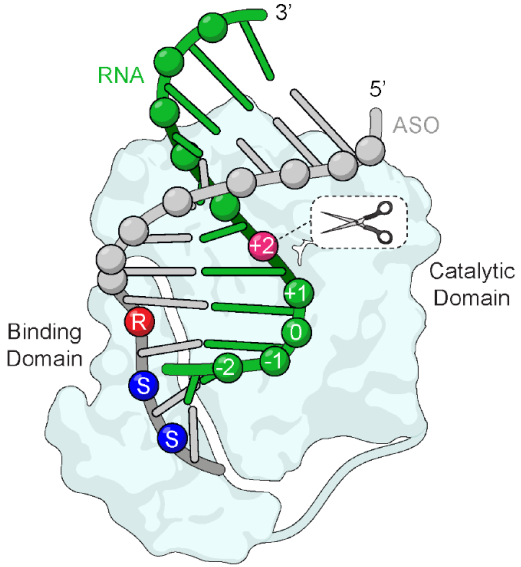
Status of the presynaptic compartment determines the integrity of the network

Presented by Dr. Frederic Saudou at Wave's Analyst and Investor Research Day on October 7, 2019
Virlogeux et al., Cell Reports 2018

Wave approach: novel, allele-selective silencing

Aims to lower mHTT transcript while leaving healthy wild-type HTT relatively intact

- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including Huntington's disease (HD)
- Potential to provide treatment for up to 80% of HD population



RNase H and ASO:RNA

Allele-selectivity possible by targeting SNPs associated with expanded long CAG repeat in HTT gene

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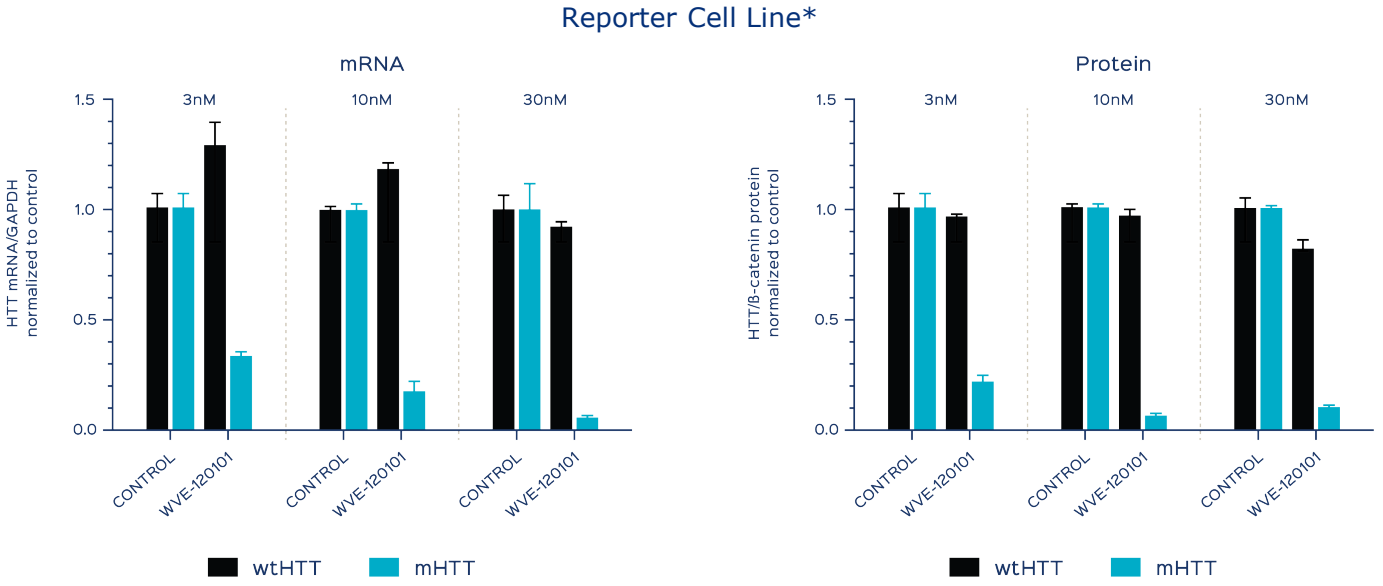
Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. *Clin Genet.* 2014;86:29–36.

Selective reduction of mHTT mRNA & protein

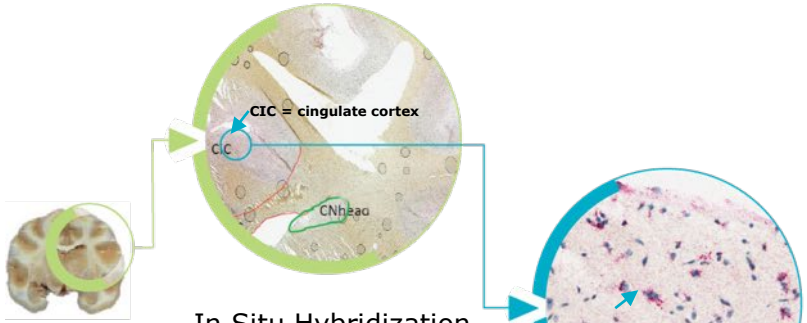


*These results were replicated in a patient-derived cell line

Source: Meena, Zboray L, Svrzikapa N, et al. Selectivity and biodistribution of WVE-120101, a potential antisense oligonucleotide therapy for the treatment of Huntington's disease. Paper presented at: 69th Annual Meeting of the American Academy of Neurology; April 28, 2017; Boston, MA.

Demonstrated delivery to brain tissue

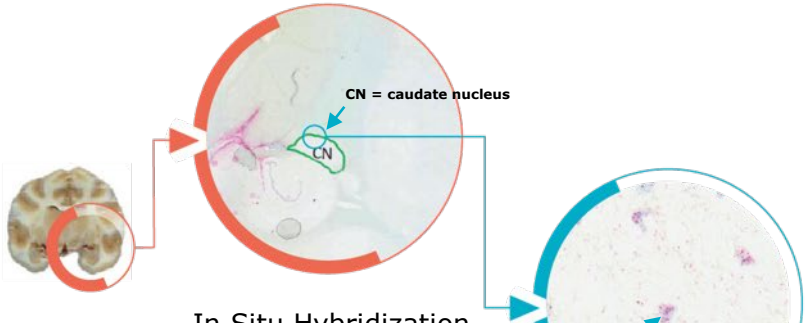
- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate brain following intrathecal bolus injection



In Situ Hybridization ViewRNA stained tissue

Red dots are WVE-120101 oligonucleotide

Arrow points to nuclear and perinuclear distribution of WVE- 120101 in cingulate cortex



In Situ Hybridization ViewRNA stained tissue

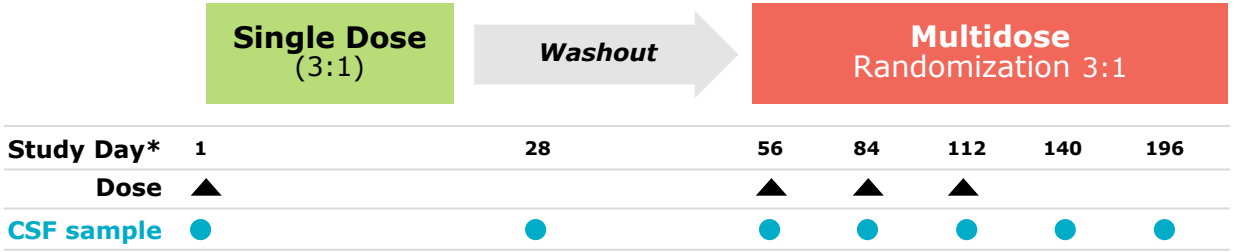
Red dots are WVE-120102 oligonucleotide

Arrow points to nuclear and perinuclear distribution of WVE-120102 in caudate nucleus

Source: Meena, Zboray L, Svrzikapa N, et al. Selectivity and biodistribution of WVE-120101, a potential antisense oligonucleotide therapy for the treatment of Huntington's disease. Paper presented at: 69th Annual Meeting of the American Academy of Neurology; April 28, 2017; Boston, MA.

PRECISION-HD clinical trial design

Two parallel, multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials for WVE-120101 and WVE-120102

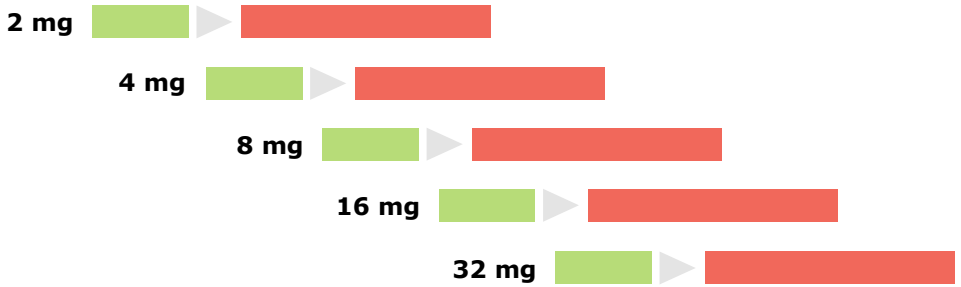


PRECISION-HD2 OLE:
Initiated October 2019

PRECISION-HD1 OLE:
Initiated February 2020

Multidose Cohorts

N = 12 per cohort



- PRECISION-HD2 data from 32 mg cohort expected in 2H 2020
- PRECISION-HD1 topline data, including 32 mg cohort, expected in 2H 2020

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OLE: Open label extension; CSF: cerebrospinal fluid *Study day may vary depending on patient washout period

PRECISION-HD2 topline results

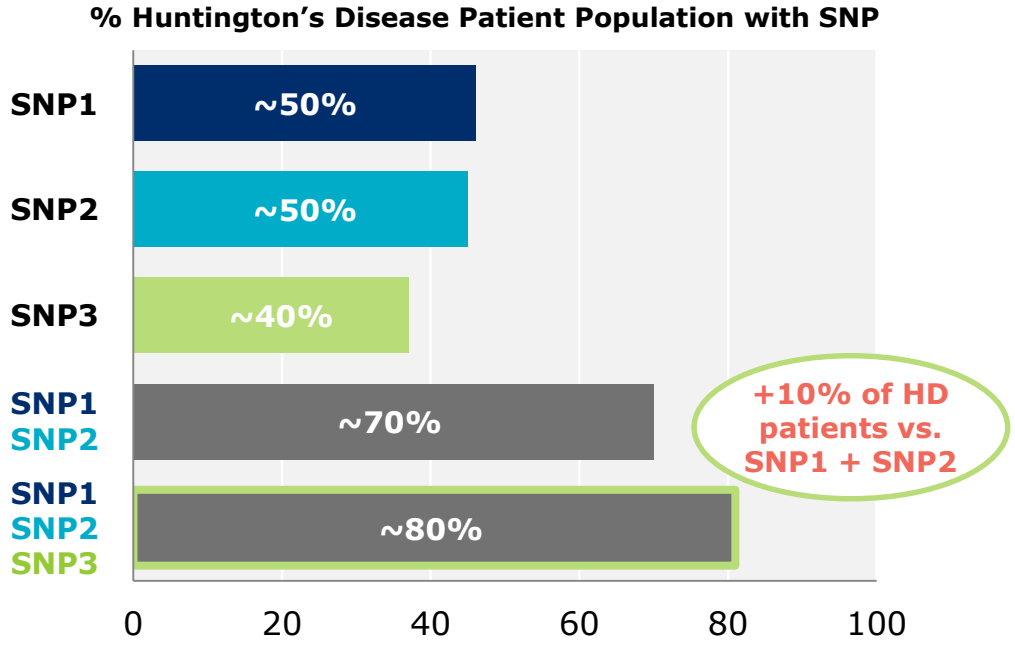
Clinical trial ongoing

Doses	Safety	Biomarker Effects	
		mHTT	wtHTT
• **WVE-120102 2–16 mg (pooled)**	• **Generally safe and well tolerated**	• **Reduction in mHTT compared to placebo (-12.4%[1], p<0.05[2])** • **Analysis across groups suggests dose response at highest doses (p=0.03)[3]**	• **No change in tHTT compared to placebo** • **Ongoing evaluation**
• 32 mg cohort initiated • Assessing the potential for higher dose cohorts	• Safety profile supports addition of higher dose cohorts	• Potential for greater mHTT reduction at higher doses	• Larger reductions of mHTT expected to result in discernible impact on tHTT

Topline results announced December 30. 2019; mHTT: mutant huntingtin wtHTT: wild-type HTT tHTT: total HTT
[1] Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo; [2] Wilcoxon-Mann-Whitney non-parametric significance test; [3] Multiple Contrast Test (MCT)

Three allele-selective HD programs

Potential to address ~80% of HD patient population



Intend to explore efficacy in early manifest and pre-manifest HD patient populations

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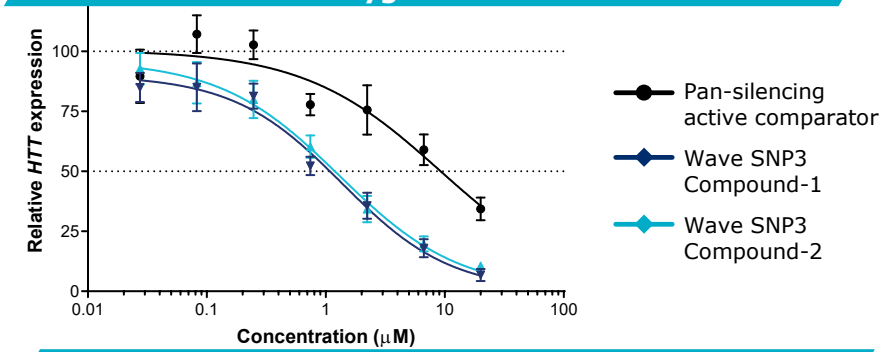
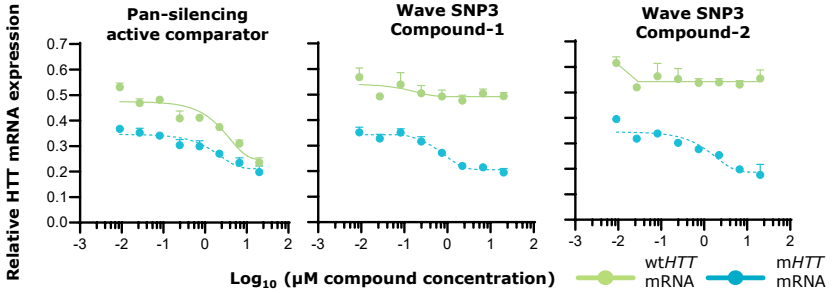
SNP3 program approaching clinical development

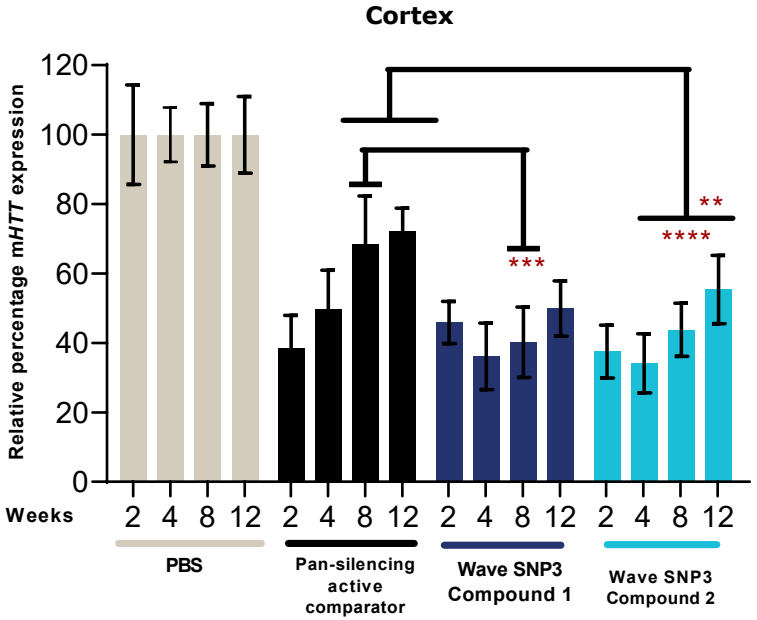
Potent mutant *HTT* knockdown activity in homozygous iCell neurons



No loss of selectivity with increasing concentrations



Knockdown persists for 12 weeks in BACHD mouse model



Similar knockdown achieved in striatum

Clinical development expected to initiate in 2H 2020

Data presented at CHDI Foundation's 15th Annual HD Therapeutics Conference Feb 24-27, 2020; See poster for full dataset.

[Figure on right] Statistics: All oligo treatment groups statistically significantly different from PBS; One-way ANOVA ****, P≤0.0001. SNP3 Compound-1 and Compound-2 significantly different from pan-silencing active comparator at 8, 12 weeks ***, P<0.005; **P=0.001."

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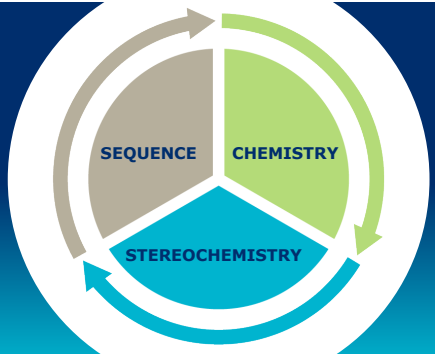
PRISM Platform

PRISM™

Enables Wave to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities

DESIGN

Unique ability to construct stereopure oligonucleotides with one defined and consistent profile



OPTIMIZE

A deep understanding of how the interplay among oligonucleotide sequence, chemistry, and backbone stereochemistry impacts key pharmacological properties

Through iterative analysis of *in vitro* and *in vivo* outcomes and artificial intelligence-driven predictive modeling, Wave continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles

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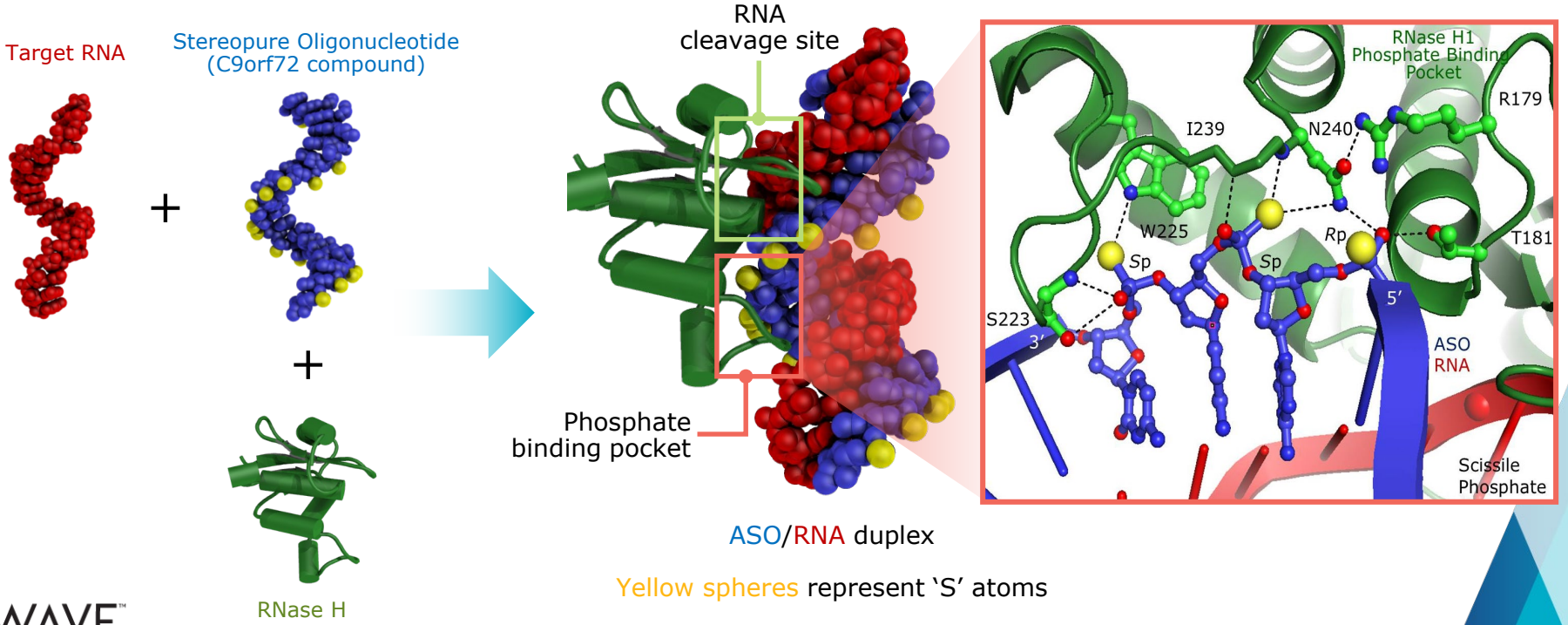
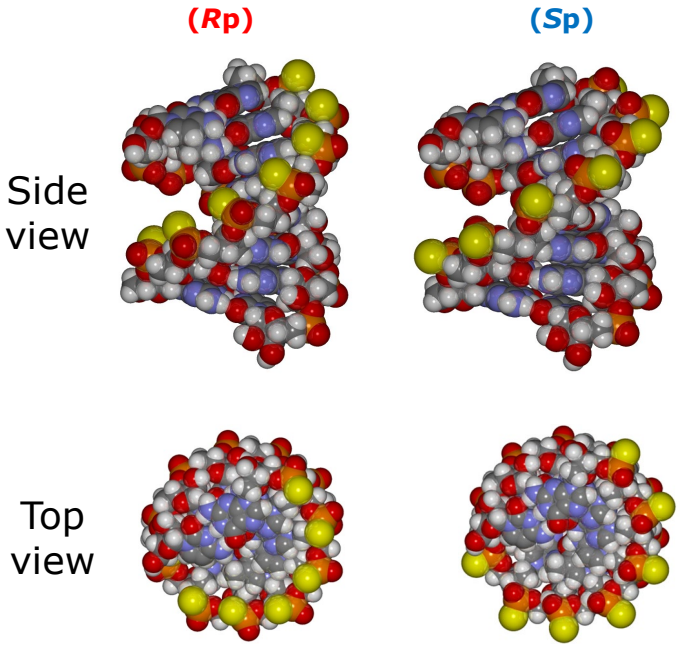
PRISM enables optimal placement of backbone stereochemistry

Crystal structure confirms phosphate-binding pocket of RNase H binds 3′-SSR-5′ motif in stereopure oligonucleotide – supports design strategy for Wave oligonucleotides

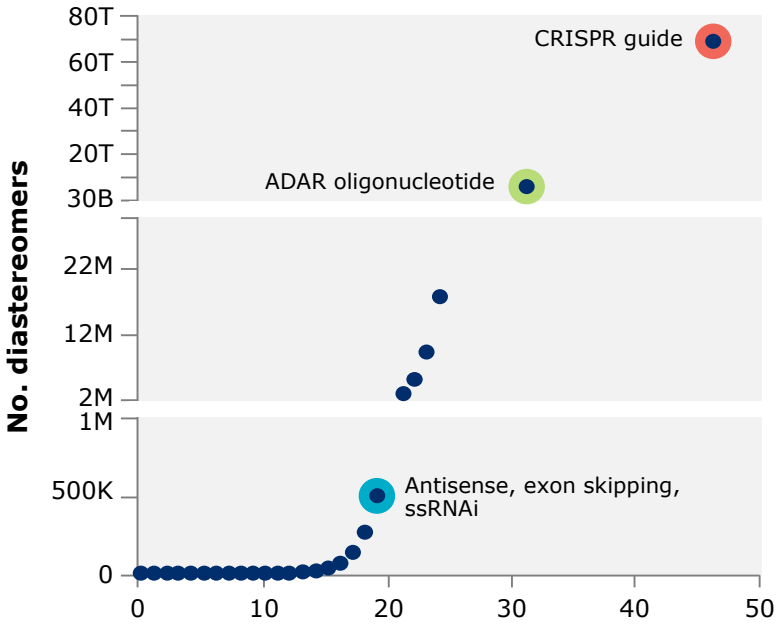


Importance of controlling stereochemistry

Stereochemical diversity



Exponential diversity arises from uncontrolled stereochemistry

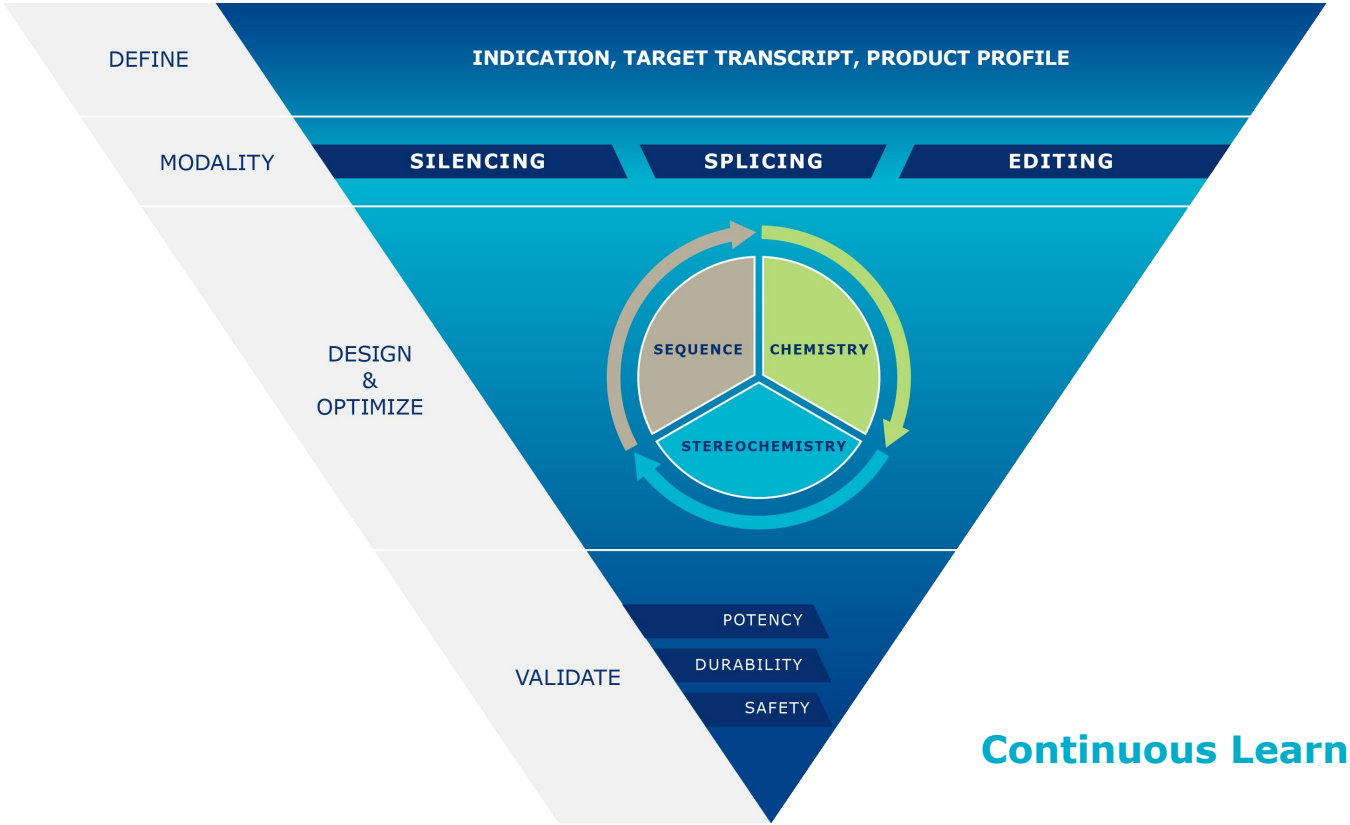


Yellow spheres represent 'S' atoms

PS: Phosphorothioate

Number of PS linkages in oligonucleotide backbone

PRISM platform enables rational drug design



Continuous Learning

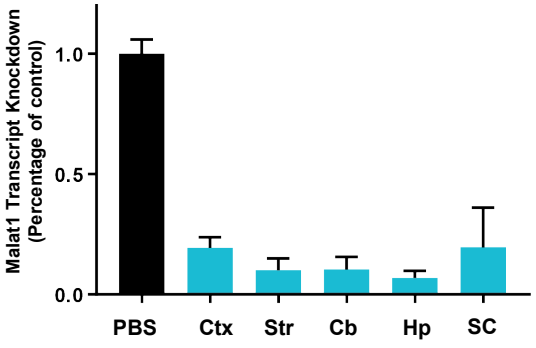
Source: Iwamoto N, et al. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. *Nat Biotechnol*. 2017;35:845-851.

Optimizing potency and durability across multiple tissues

CNS

Malat1 Transcript Knockdown in Mice

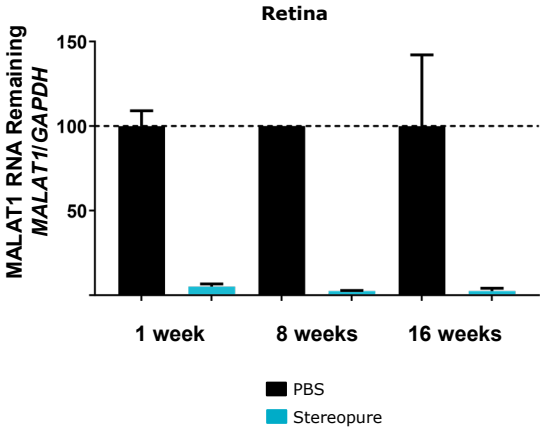
10 Weeks after single 100 µg ICV injection



Eye

MALAT1 Knockdown in Non-Human Primates

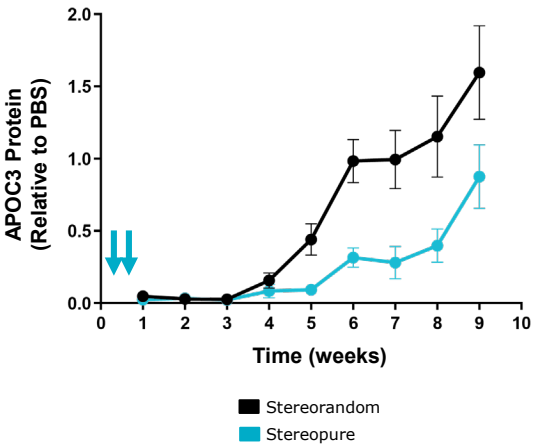
Single 450 µg IVT injection



Liver

Knockdown of Serum APOC3 Protein Levels in Mice

Two 5 mg/kg SC injections on Days 1&3



Data represented in this slide from *in vivo* studies. CNS: PBS = phosphate buffered saline; Ctx = cortex; Str = striatum; Cb = cerebellum; Hp = hippocampus; SC = spinal cord. ICV = intracerebral; IVT = intravitreal; IV = intravenous; SC= subcutaneous.

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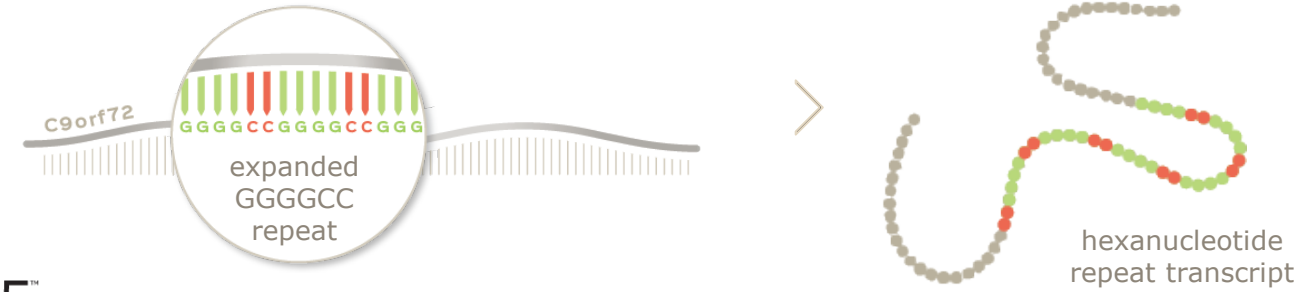
C9orf72 program

Amyotrophic Lateral Sclerosis (ALS)

Frontotemporal Dementia (FTD)

C9orf72: a critical genetic risk factor

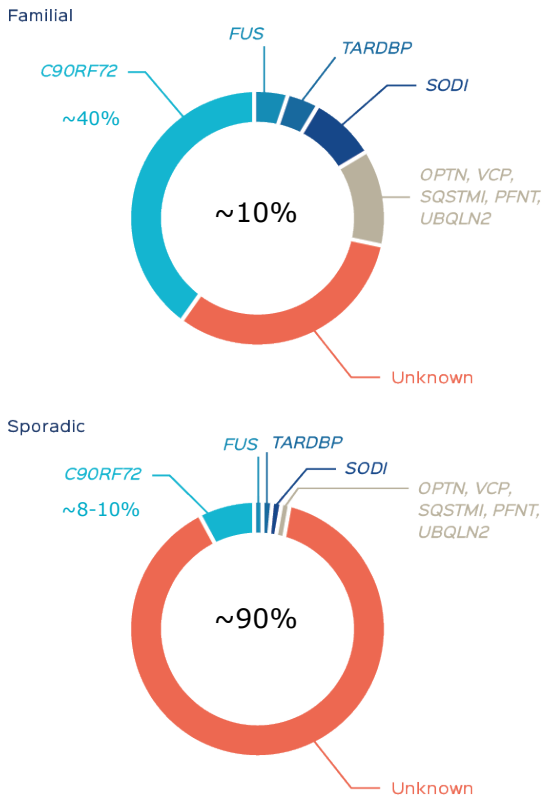
- C9orf72 gene provides instructions for making protein found in various tissues, with abundance in nerve cells in the cerebral cortex and motor neurons
- C9orf72 genetic mutations are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD); GGGGCC repeat drives the formation and accumulation of dipeptide repeat proteins that accumulate in brain tissue
- First pathogenic mechanism identified to be a genetic link between familial (inherited) ALS and FTD
- Most common mutation identified associated with familial ALS and FTD
- Availability of dipeptide biomarker in CSF has potential to accelerate drug development



Source: DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. *Neuron.* 2011;72:245-256. Renton AE, Majounie E, Waite A, et al. *Neuron.* 2011;72:257-268.

Amyotrophic lateral sclerosis

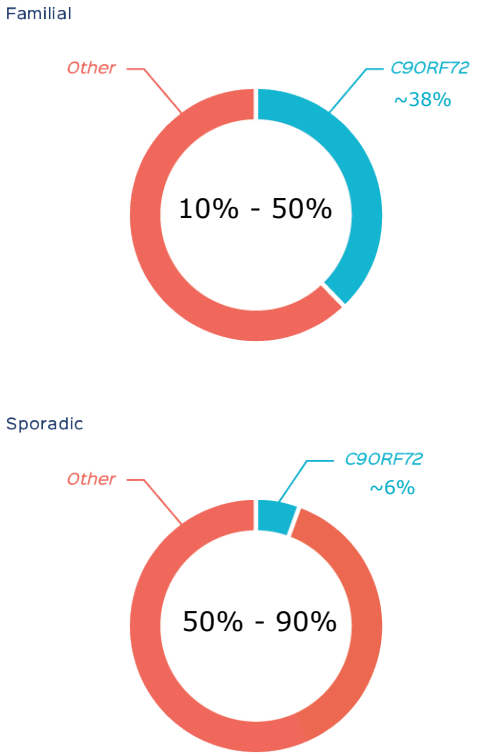
- Fatal neurodegenerative disease characterized by the progressive degeneration of motor neurons in the brain and spinal cord
- Affects approximately 15,000-20,000 people in the US with a median survival of three years
- C9orf72 is present in approximately 40% of familial ALS and 8-10% of sporadic ALS; currently the most common demonstrated mutation related to ALS, far more so than SOD1 or TDP-43
- Pathogenic transcripts of the C9orf72 gene contain hundreds to thousands of hexanucleotide repeats compared to 2-23 in wild-type transcripts; dominant trait with high penetrance



Source: Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. *Nat Neurosci*. 2014;17:17–23.

Frontotemporal dementia

- Progressive neuronal atrophy with loss in the frontal and temporal cortices characterized by personality and behavioral changes, as well as gradual impairment of language skills
- Affects approximately 55,000 people in the US
- Second most common form of early-onset dementia after Alzheimer's disease in people under the age of 65
- Up to 50% of FTD patients have a family history of dementia, many inheriting FTD as an autosomal dominant trait with high penetrance
- Pathogenic transcripts of the C9orf72 gene contain hundreds to thousands of hexanucleotide repeats compared to 2-23 in wild-type transcripts



Sources: Stevens M, et al. Familial aggregation in frontotemporal dementia. *Neurology.* 1998;50:1541-1545. Majounie E, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol.* 2012;11:323-330.

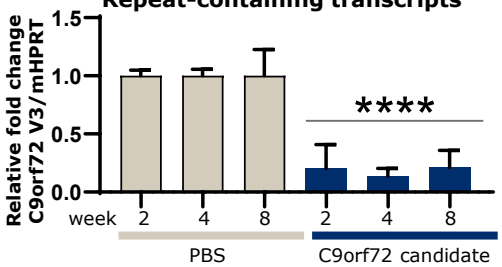
C9orf72 program: Selective silencing *in vivo* of expanded C9orf72 repeat transcripts

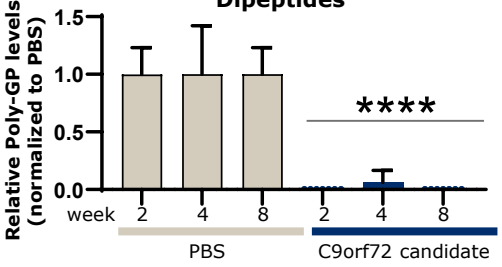
- C9orf72 genetic mutations are the most common cause of familial Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) and are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of ALS and FTD; Hexanucleotide repeat drives the formation and accumulation of dipeptide repeat proteins that accumulate in brain tissue
- **Wave's approach:** Selectively silence the repeat containing transcript while minimizing the impact on C9orf72 protein

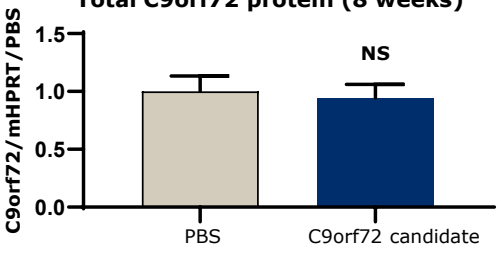
Potent *in vivo* knockdown of repeat containing transcripts and dipeptides

Protein preservation

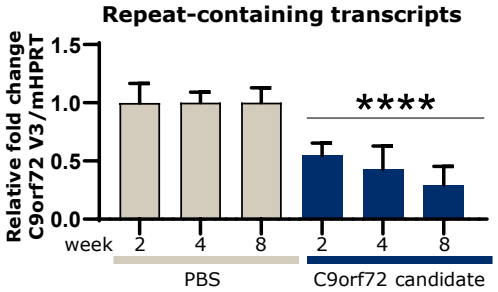
Spinal Cord

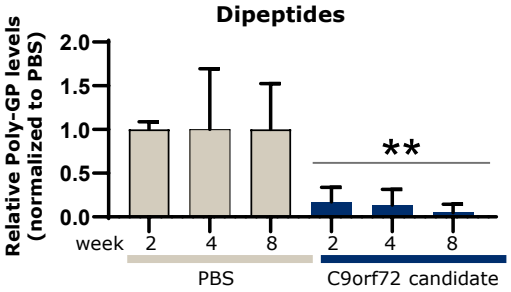


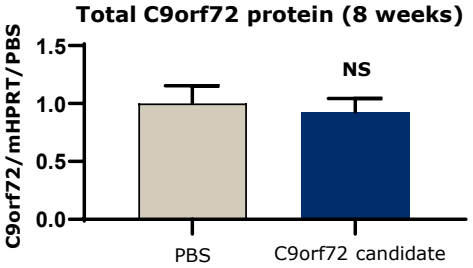




Cortex







Clinical development expected to initiate in 2H 2020

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Experimental description: 2 x 50 ug on day 1 and day 8; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Protein samples were measured by Western Blot. Dipeptide repeat proteins were measured by Poly-GP MSD assay.

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Ophthalmology

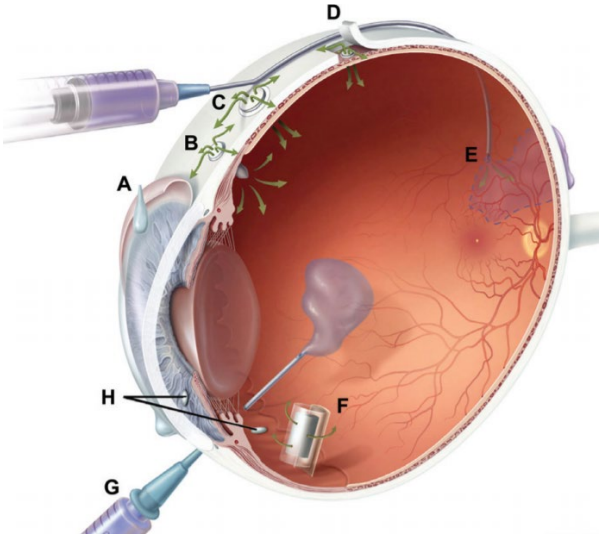
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

Wave ophthalmology opportunity

- Oligonucleotides can be administered by intravitreal (IVT) injection; targeting twice per year dosing
- Stereopure oligonucleotides open novel strategies in both dominant and recessive IRDs; potential for potent and durable effect with low immune response

Successful targeting of *MALAT1* is a surrogate for an ASO mechanism of action

- Widely expressed in many different cell types
- Only expressed in the nucleus



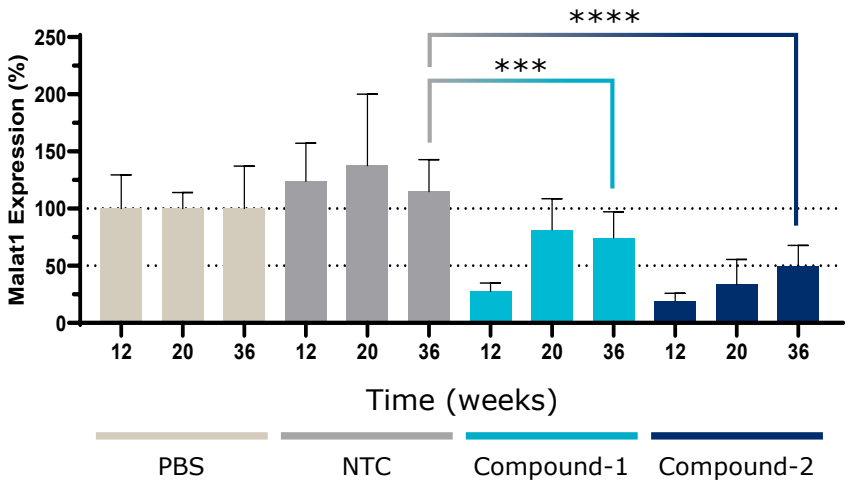
Intravitreal injection

Sources: Daiger S, et al. *Clin Genet*. 2013;84:132-141. Wong CH, et al. *Biostatistics*. 2018; DOI: 10.1093/biostatistics/kxx069. Athanasiou D, et al. *Prog Retin Eye Res*. 2018;62:1–23. Daiger S, et al. *Cold Spring Harb Perspect Med*. 2015;5:a017129. Verbakel S, et al. *Prog Retin Eye Res*. 2018:66:157-186.; Short, B.G.; *Toxicology Pathology*, Jan 2008.

Stereopure compound induces potent and durable *MALAT1* knockdown in the eye

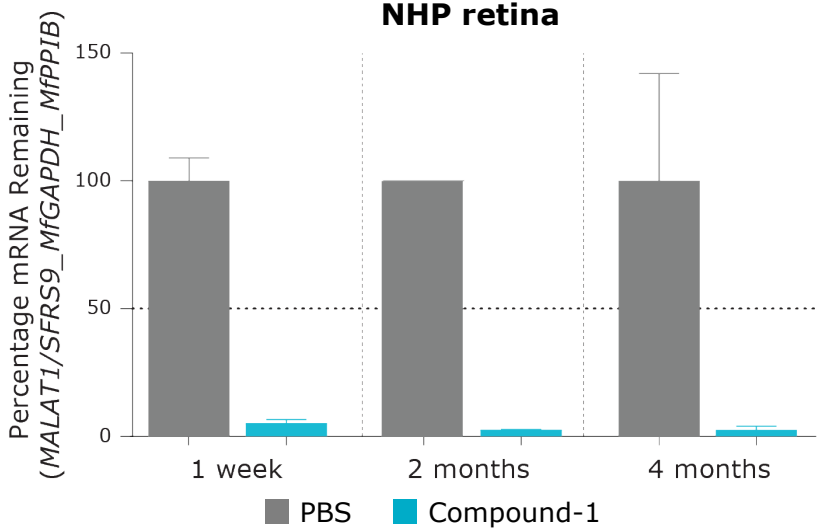
~50% *MALAT1* knockdown at 9 months

In vivo duration of effect in the mouse retina



>90% knockdown of *MALAT1* maintained for 4 months

In vivo duration of effect in the NHP retina



Mouse: Compound or PBS (1 x 50 mg IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. Statistics: Compound-2 Malat1 levels are significantly different from NTC at 36 weeks ***, P<0.001; **** P<0.0001, respectively. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control; Compound-1 and Compound-2 are stereopure MALAT1-targeting antisense oligonucleotide. NHP: Oligonucleotide or PBS (1 x 450 μg IVT) was delivered to NHP. Relative percentage of *MALAT1* RNA in the retina to PBS-treated is shown at 1 week, 2 and 4 months, post-single injection. Compound-1 is a stereopure *MALAT1*-RNA-targeting antisense oligonucleotide.

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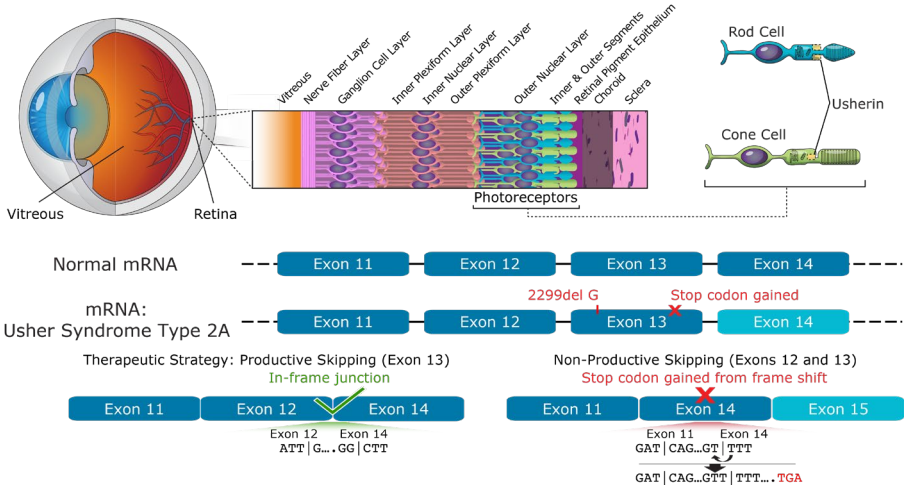
Usher Syndrome Type 2A: a progressive vision loss disorder

- Autosomal recessive disease characterized by hearing loss at birth and progressive vision loss beginning in adolescence or adulthood
- Caused by mutations in USH2A gene (72 exons) that disrupt production of usherin protein in retina, leading to degeneration of the photoreceptors
- No approved disease-modifying therapies
- **~5,000 addressable patients in US**



Oligonucleotides that promote USH2A exon 13 skipping may restore production of functional usherin protein

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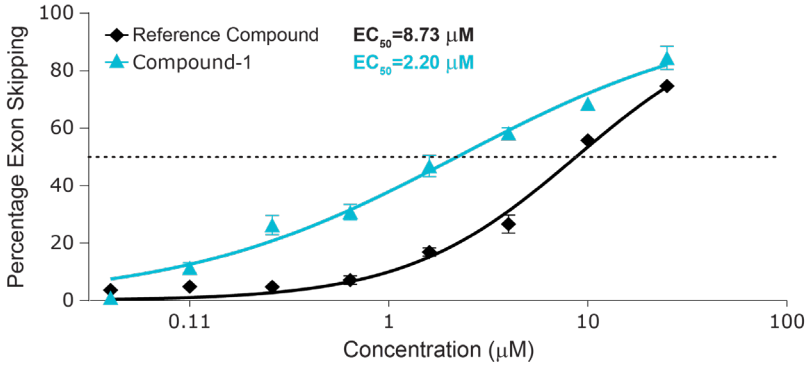
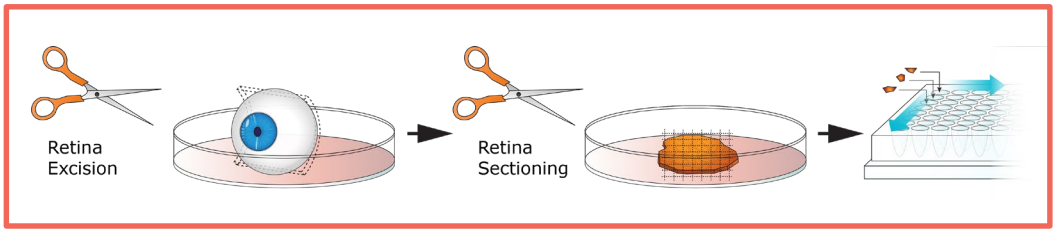
Sources: Boughman et al., 1983. *J Chron Dis*. 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

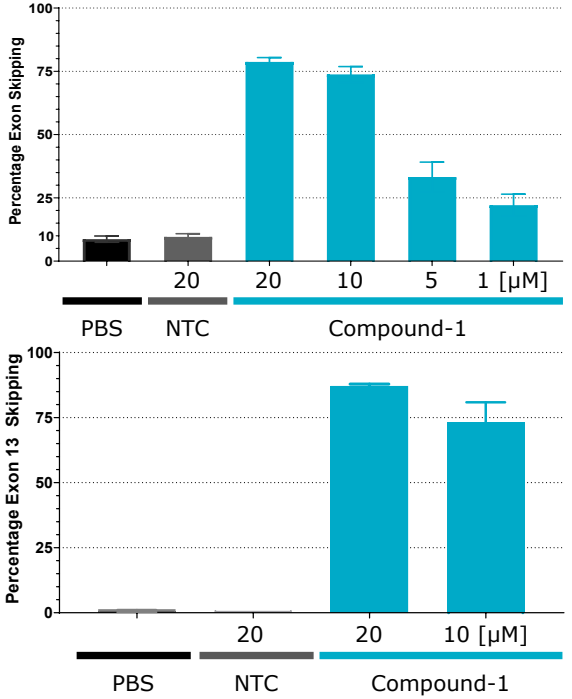
Potent USH2A exon 13 skipping with stereopure compound in *vitro* and *ex vivo*

Enhanced potency over a stereorandom reference compound (*in vitro*)





Target engagement in NHP and human retinas (*ex vivo*)

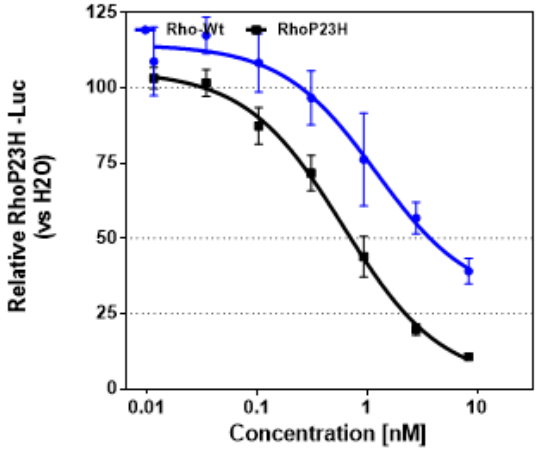


Left: Compounds were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. *USH2A* transcripts were normalized to *SRSF9*. Data are mean±s.d., n=2. Reference Compound: van Diepen *et al.* 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide. Right: Whole NHP and human eyes were enucleated (n=4 and n=2, respectively) and compounds (1–20 µM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by 48 hrs later by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m.

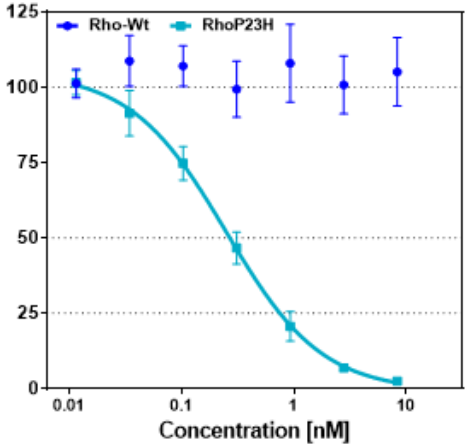
Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

- **Retinitis pigmentosa (RP)**: group of rare, genetic eye disorders resulting in progressive photoreceptor cell death and gradual functional loss; currently no cure
- ~10% of US autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO)
- Mutant P23H rhodopsin protein is thought to misfold and co-aggregate with wild-type rhodopsin, resulting in a gain-of-function or dominant negative effect in rod photoreceptor cells

Stereorandom



Stereopure



In vivo

Collaborations in place for evaluation in transgenic human Rho P23H pig model

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Ferrari et al., *Current Genomics.* 2011;12:238-249.; Reporter assays on a Wave stereopure sequence as well as a sequence described in WO2016138353A1: ASO and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells are harvested, and relative luminescence is measured.

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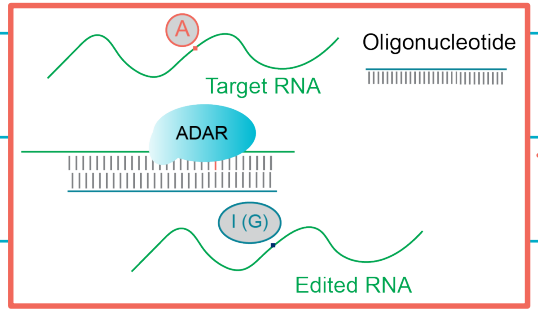
ADAR-mediated RNA editing

RNA-editing can be used for several therapeutic applications and supplement Wave's existing modalities

Strategy	Therapeutic Application	Treatment Modality: Silencing	Splicing	RNA Editing
Silence protein expression	Reduce levels of toxic mRNA/protein	✓		✓
Alter mRNA splicing	Exon skipping/inclusion/ restore frame		✓	✓
Fix nonsense mutations that cannot be splice-corrected	Restore protein expression			✓
Fix missense mutations that cannot be splice-corrected	Restore protein function			✓
Modify amino acid codons	Alter protein function			✓
Remove upstream ORF	Increase protein expression			✓



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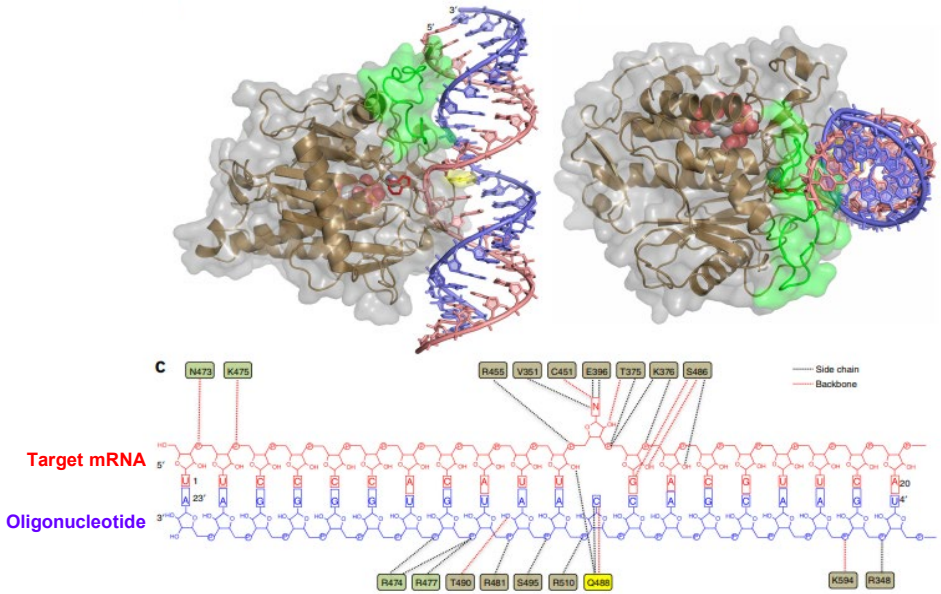
I (G): ADAR converts A>I, I is recognized as G by all cellular machinery; ADAR: Adenosine Deaminase Acting on RNA; ORF: Open reading frame

Using PRISM to unlock ADAR-mediated RNA editing

Structure of ADAR deaminase domain bound to dsRNA substrate



- ADAR makes multiple contacts with oligonucleotide backbone, sugar and bases
- Using PRISM platform, rationally designed and screened oligonucleotides to optimize:
  - 2' sugar chemistry
  - Backbone chemistry and stereochemistry
  - Size and structure
  - Modified nucleobases

~1,000 RNA editing oligonucleotides tested over the last year to develop SAR for editing format

Structure adapted from Matthews et al., Nat Struct Mol Biol. (2016); SAR = structure-activity relationship; ADAR: Adenosine Deaminase Acting on RNA; dsRNA = double-stranded RNA

Wave's ADAR approach has several potential advantages over existing technologies

Existing RNA editing technologies		Wave's RNA editing platform
Use unmodified RNA	Stability	Fully chemically-modified stereopure oligonucleotides
Require AAV or lipid nano particle delivery	Delivery	Free uptake into tissues
Require exogenous protein (e.g. CAS13 or chimeric ADAR)	Editing	Uses endogenous ADAR for editing

Single oligonucleotide through free uptake is sufficient for editing

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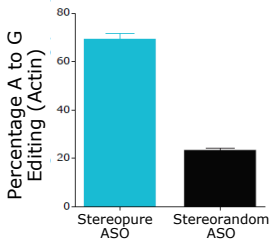
RNA Editing with Endogenous ADAR Achieved Across Multiple Primary Human Cell Types

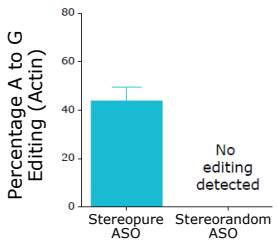
Editing of Up to 70% Achieved *In Vitro*

Editing UAG Site in Actin mRNA in Primary Human Cell Lines

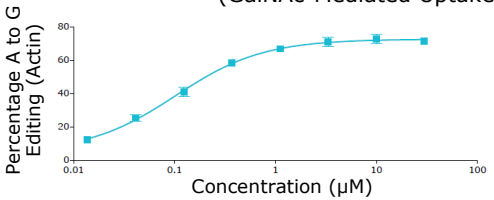
Hepatocytes
(Gymnotic Uptake)



Bronchial Epithelial Cells
(Gymnotic Uptake)



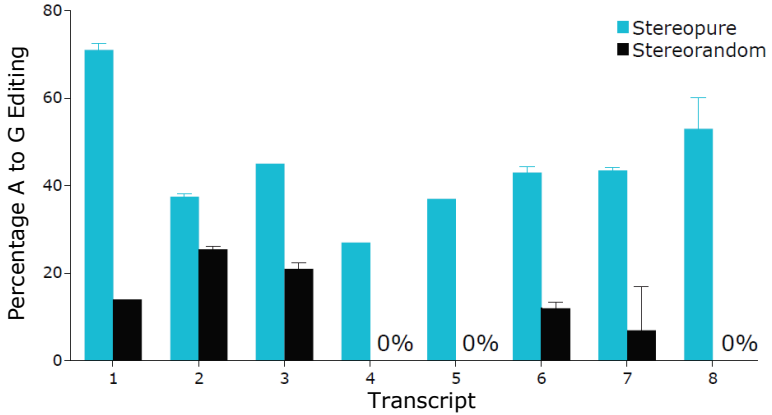
Targeting Editing in Primary Human Hepatocytes
(GalNAc-Mediated Uptake)



- Dose dependent RNA editing with EC_{50} of ~100 nM

Technology Validated Across Multiple Sequences *In Vitro*

Editing in Primary Human Hepatocytes

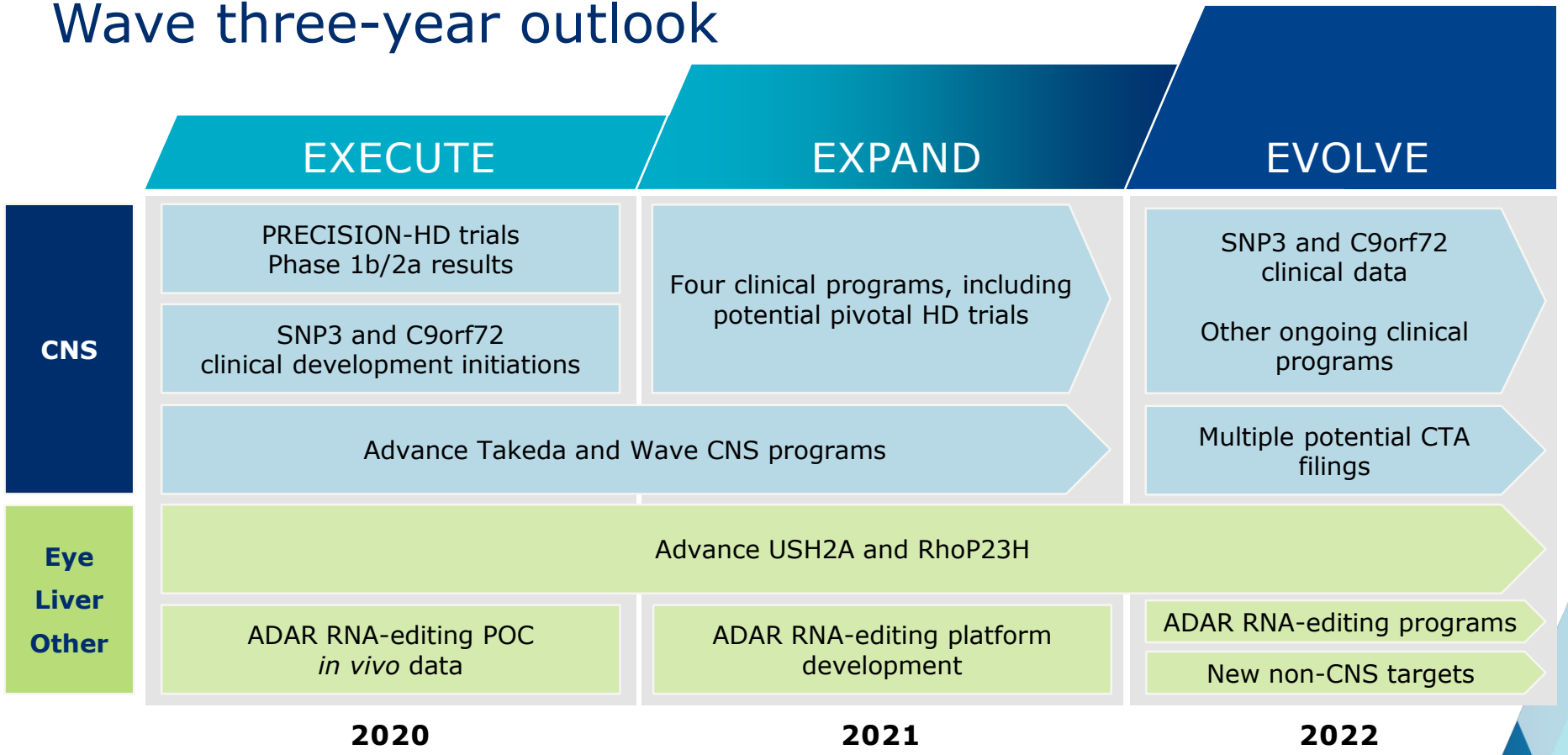


- Editing achieved across several distinct RNA transcripts

In vivo editing data with fully modified stereopure oligonucleotides expected in 2020

Data presented at 1st International Conference on Base Editing – Enzymes and Applications (Deaminet 2020); See poster for full dataset

Wave three-year outlook



PRISM **Chemistry innovations transferred to new programs**

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POC: proof of concept

Anticipated upcoming Wave milestones

CNS

- **2H 2020:** PRECISION-HD2 data from 32 mg cohort in Huntington's disease
- **2H 2020:** PRECISION-HD1 topline data, including 32 mg cohort, in Huntington's disease
- **2H 2020:** Initiate clinical development of SNP3 program in Huntington's disease
- **2H 2020:** Initiate clinical development of C9orf72 program in ALS and FTD

Ophthalmology

- **2020:** Advance USH2A and RhoP23H programs

RNA-editing

- **2020:** *In vivo* ADAR editing data

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Realizing the potential of genetic medicines

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